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(54) Title: PARASITICIDAL COMPOSITION

(57) Abstract: The invention relates to a parasiticidal composition comprising a terpene or derivative thereof having parasiticidal activity, a naturally occurring plant saponin and a physiologically acceptable carrier.

PARASITICIDAL COMPOSITION

The invention relates to a parasiticidal composition and in particular to a composition for controlling headlice infestation in humans.

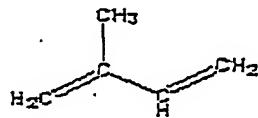
Lice infestation in man is generally caused by insects from the families *Pediculidae* and *Pthiridae*, in particular *Pediculus humanus* species and *Pthirus pubis*.

The control of parasite infestations such as headlice has recently been managed by mosaic policies, with insecticides from the groups consisting DDT, cyclodienes, organophosphates, carbamates and pyrethroids.

To ensure the availability of as many insecticidal treatments as possible there is a continuing requirement for novel insecticides to ensure suitable mosaic policies are maintained.

It is an object of the present invention to seek to provide an alternative novel insecticide for the treatment of headlice.

Terpenes are classed as a group of hydrocarbons that are made up of building blocks of isoprene or similar five-carbon units, with a monoterpene made up of two units (example: limonene and pinene), a sesquiterpene made up of three units (example: humulene,), and a diterpene made up of four units (example: phytol).



Isoprene

The Isoprene rule was first pointed out by Wallach (1887) and it was later elucidated by Ingold (1925) who discussed that isoprene units in natural terpenes were joined "head-to-tail".

The terpenes, in our context, are the primary constituents in the aromatic fractions of scented plants, generally essential oils, flavours and fragrances. The extraction and synthesis of compounds such as these is the basis for the perfumery industry and they find a variety of uses in the feed and pharmaceutical industry as flavour and odour improvers, such as Limonene and Terpineol.

Saponin molecules are a combination of a sugar chain attached to either a sterol or a triterpene. Their name is derived from their ability to form foams in water, which is a function of a molecule containing both water (sugar) and fat soluble (triterpene) components. They are found in many plants, but get their name from the soapwort plant. Saponins at a concentration of about 5.6% are frequently employed in soap, shampoo and bath salt formulation.

According to the invention there is provided a parasiticidal composition, comprising a terpene or derivative thereof having parasiticidal activity, a naturally occurring plant saponin, and a physiologically acceptable carrier.

The terpene or derivative may comprise one or more of d-limonene, geranyl acetate and eugenol, and the plant saponin may comprise one or more from the group consisting of Peru balsam, yucca, soapwort, ginseng and quillija.

It is preferred that the composition is adapted for topical application to a subject. It is particularly preferred that the composition is adapted for application as a lotion or mousse for the hair.

The composition may comprise an alcohol, such as isopropanol and/or ethanol, and the physiologically acceptable carrier may comprise the alcohol.

The composition may comprise at least about 1.0% v/v terpene or derivative.

It is preferred that the composition is for use in the treatment and/or prevention of human infestation by parasites from the families *Pediculidae* and *Pthiridae*.

According to a further aspect of the invention there is provided a process for preparing a parasiticidal composition, which comprises bringing a terpene or derivative thereof and a naturally occurring plant saponin into association with at least one physiologically acceptable carrier therefor.

According to a yet further aspect of the invention there is provided the use of a terpene or derivative thereof and a plant saponin in the manufacture of a composition for use in controlling parasite infestations in humans, in particular infestation by parasites from the families *Pediculidae* and *Pthiridae*.

The invention will further be described by way of illustration by reference to the following experiments.

Method of Testing the Pediculicidal Activity of a Composition.

A composition comprising eugenol and the saponin soapwort was prepared. In preparation for use the stock chemicals were diluted to the appropriate level using 60% propan-2-ol (isopropyl alcohol, isopropanol) diluted with 40% distilled water.

Solutions of the eugenol and soapwort were made on a weight for weight basis (w/w) in the alcohol vehicle.

Measurement of Pediculicidal Activity by Immersion.

Human lice, *pediculus humanus*, were obtained from the culture colony maintained by the Medical Entomology Centre. Adult female and male lice, in approximately equal numbers, were used for each test. The lice were fed on the morning of the test and allowed a minimum of 4 hours to recover, during which time they were able to excrete excess water imbibed with their blood meal. Lice were counted into batches that were provided with squares of an open meshed nylon gauze (tulle), as a substrate upon which to stand, and each batch allocated to a marked 30 millimetre plastic Petri dish.

For the test procedure an aliquot of approximately 5 millilitres of the test solution was poured into the base of a clean 30 millimetre plastic Petri dish. The gauze bearing lice was immersed in the fluid for 10 seconds, during which time the gauze was turned at least twice to ensure removal of air bubbles. After removal from the fluid the gauze and insects were lightly blotted to remove

excess fluid and returned to their marked Petri dish. The same procedure was repeated for the other replicate gauze squares in that batch.

Gauze squares bearing lice were incubated under normal maintenance conditions ($30^{\circ} \pm 2^{\circ}$ Celsius and $50\% \pm 15\%$ relative humidity) for the remainder of the test period. At the end of exposure period the insects and gauze were washed using a bland toiletry shampoo (Boots frequent wash shampoo) diluted one part shampoo with fourteen parts water (FWS 1:15) after which they were rinsed three times using 250 millilitres of warm (34° Celsius) tap water poured through and over the gauze squares. They were then blotted dry using medical wipe tissue and incubated under normal maintenance conditions in clean plastic Petri dishes of the appropriate size until the results were recorded.

For these tests lice were exposed for 2 hours.

A control comparison test was performed using the 60% propan-2-ol (isopropanol) solvent, which is routinely used in our laboratory and causes minimum mortality to lice, in place of the test solution and a 0.5% eugenol solution. All other procedures for this comparator were the same as for the test groups.

The results of tests against lice were recorded after 24 hours.

Results

Activity of the test solution against lice was effectively complete with 0.5% solutions. Dead lice showed signs of dehydration and most had burst guts so that they took on a dark red colour throughout the tissues.

Treatment	Replicate	Number of lice		Mortality %	
		Total	Killed	Moribund	
10% (water)					
Soapwort	1	21	1	2	15
Peru Balsam	1	20	0	3	15
Yucca	1	20	1	1	10
Eugenol 0.5%	1	21	3	3	36.6
0.5% Eugenol with Soapwort	1	21	18	3	100

Mortality percentages were corrected by Abbott's formula. The percent of mortality in a control was subtracted from the percent mortality in the test and then divided by the percent mortality in the test.

Formulation

Using the results of these tests, formulations having parasiticidal activity were prepared as follows:

Lotion Formulation

Eugenol	0.5%
Soapwort	0.5%
Water	30.0%

Isopropyl Alcohol to 100%

Mousse Formulation

Eugenol	0.5%
Soapwort	0.5%
Polawax	4.0%
Crodamol DA	2.0%
Propylene Glycol	2.0%
Polysorbate 60	1.0%
Sodium Lauryl Sulphate	0.5%
Isopropyl Alcohol	5.0%
Water	79.5%
Butane	5.0%

Thus, formulations which can be prepared in accordance with this invention include lotions and mousses as well as, potentially, other hair treatments. The precise nature and qualities of additional constituents which are required will vary according to the desired properties of the final product. The skilled worker will be familiar with such constituents and their usage, which can include, for example, surfactants, silicone compounds, suspending agents colourings and perfumes.

CLAIMS:

1. A parasiticidal composition, comprising a terpene or derivative thereof having parasiticidal activity and a naturally occurring plant saponin in a physiologically acceptable carrier.
2. A composition according to claim 1, wherein the terpene comprises one or more of d-limonene, geranyl acetate and eugenol.
3. A composition according to claim 1 or claim 2, wherein the saponin comprises one or more of peru balsam, yucca, soapwort, ginseng or quillija.
4. A composition according to any preceding claim, adapted for topical application to a subject.
5. A composition according to claim 4, adapted for application as a lotion or a mousse.
6. A composition according to any preceding claim, further comprising alcohol.
7. A composition according to claim 6, wherein the physiologically acceptable carrier comprises the alcohol.
8. A composition according to claim 6 or claim 7, the alcohol comprising isopropanol and/or ethanol.

9. A composition according to any preceding claim, comprising at least about 0.5% v/v terpene or derivative thereof and 0.5% plant saponin.
10. A composition according to any preceding claim, for use in the treatment and/or prevention of human infestation by parasites from the families *Pediculidae* and *Pthiridae*.
11. A composition according to any preceding claim, comprising a terpene or derivative thereof, a naturally occurring plant saponin, water and isopropyl alcohol in the form of a lotion.
12. A composition according to any of claims 1 to 10, comprising a terpene or derivative thereof, a naturally occurring plant saponin, polawax, crodamol DA, propylene glycol, polysorbate 60, sodium lauryl sulphate, isopropyl alcohol, water and butane in the form of a mousse.
13. A process for preparing the parasiticidal composition claimed in any of claims 1 to 12, which comprises bringing a terpene or derivative thereof having parasiticidal activity and a plant saponin into association with at least one physiologically acceptable carrier therefor.
14. A process according to claim 13, wherein the composition comprises a lotion or mousse.

15. A process according to claim 13 or claim 14, further including the step of bringing the terpene or derivative and plant saponin into contact with an alcohol.
16. A process according to any of claims 13 to 15 which is a process for preparing a composition for use in the treatment of human infestation by parasites from the families *Pediculidae* and *Pthiridae*.
17. The use of a terpene or derivative thereof having parasiticidal activity and a plant saponin in the manufacture of a composition for use in the treatment of parasite infestation.
18. The use according to claim 17, wherein the composition is for use in the treatment of infestation in humans by parasites from the families *Pediculidae* and *Pthiridae*.

INTERNATIONAL SEARCH REPORT

national Application No PCT/GB 01/02609
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According to International Patent Classification (IPC) or to both national classification and IPC	
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B. FIELDS SEARCHED	
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Minimum documentation searched (classification system followed by classification symbols) IPC 7 A01N	
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched	
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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)	
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CHEM ABS Data, EPO-Internal, PAJ, WPI Data, BIOSIS	
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C. DOCUMENTS CONSIDERED TO BE RELEVANT	
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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 977 186 A (FRANKLIN LANNY UDELL) 2 November 1999 (1999-11-02) column 1, paragraphs 2,4,5 column 7, paragraph 1 ---	1-18
X	EP 0 495 684 A (CLILCO LTD) 22 July 1992 (1992-07-22) the whole document ---	1-18
X,Y	GB 1 467 419 A (INCHCAPE CHEMCO LTD) 16 March 1977 (1977-03-16) the whole document ---	1-18
X	WO 98 27812 A (EMERSON RALPH W ; PROGUARD INC (US); CRANDALL BRADFORD G JR (US)) 2 July 1998 (1998-07-02) page 21, paragraph 1; claims 17-20 ---	1-18 -/-

<input checked="" type="checkbox"/>	Further documents are listed in the continuation of box C.
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<input checked="" type="checkbox"/>	Patent family members are listed in annex.
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Date of the actual completion of the international search	Date of mailing of the international search report
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27 July 2001	13/08/2001
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Name and mailing address of the ISA	Authorized officer
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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bertrand, F
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INTERNATIONAL SEARCH REPORT

ational Application No
PCT/GB 01/02609

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A.Y.LEUNG,S.FOSTER: "Encyclopedia of Common Natural Ingredients used in food, drugs and cosmetics" 1996 , JOHN WILEY & SONS, INC. XP002173347 page 277 -page 281 -----	1,3,4
Y		1-18
X	S.DHARMANANDA: "Platycodon and other Chinees herbs with triterpene glycosides" INTERNET ARTICLE, 'Online! XP002173346 Retrieved from the Internet: <URL: http://www.itmonline.org/pdf/platygly.pdf > 'retrieved on 2001-07-27! the whole document -----	1,3,4

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No

PCT/GB 01/02609

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